

**AMENDMENTS TO THE CLAIMS**

This listing of claims will replace all prior versions, and listings, of claims in the application: **(AS ON AMENDED SHEET(S) ANNEXED TO IPER)**

Claims 1-19. (cancelled)

20. (new) A method for determining the suitability of a candidate compound for use in the treatment of negative symptoms of and/or cognitive dysfunction in schizophrenia, refractory schizophrenia, suicidality or mild cognitive impairment which comprises:

- a) assessing the affinity of the compound at the 5-HT<sub>2C</sub> receptor;
- b) assessing the affinity of the compound at at least two other major sites of said compound interaction;
- c) applying the assessed affinities to the following formula:

$$\begin{array}{ccccc} X & & X & & \\ - & + & - & = & Y \\ A & & B & & \end{array}$$

{wherein: X is the affinity of a compound for interaction at the 5-HT<sub>2C</sub> receptor and A and B are the average affinity values of a compound for interaction at two major sites other than the 5-HT<sub>2C</sub> receptor};

and selecting compounds in which  $Y \geq 1.80$  as suitable compounds for the treatment of cognitive dysfunction in and/or negative symptoms of schizophrenia, refractory schizophrenia, suicidality or mild cognitive impairment, provided that:

(a) for the treatment of cognitive dysfunction in and/or negative symptoms of schizophrenia or refractory schizophrenia, the compound selected is other than ritanserin, clozapine, fluperlapine, loxapine, ORG-5222, pipamperone, sertindole, olanzapine, zotepine or ziprasidone;

(b) for the indications cognitive dysfunction in schizophrenia or mild cognitive impairment, the 5-HT<sub>2C</sub> receptor antagonist is other than (1R,2S,4R)-(-)-2-phenyl-2-(dimethylaminoethoxy)-1,7,7-trimethyl-bicyclo[2.2.1]heptane, (1R,2S,4R)-(-)-2-phenyl-2-(methylaminoethoxy)-1,7,7-trimethyl-bicyclo[2.2.1]heptane and pharmaceutically acceptable acid addition salts thereof; and

(c) for the treatment of schizophrenic suicidality, the compound selected is other than clozapine.

21. (new) The method of claim 20 in which A and B are different and are independently selected from the group consisting of the 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>3</sub>, 5-HT<sub>6</sub>, 5-HT<sub>7</sub>, D<sub>1</sub>, D<sub>2-S</sub>, D<sub>2-L</sub>, D<sub>3</sub>, D<sub>4</sub>, D<sub>5</sub> M<sub>1</sub>, M<sub>2</sub>, M<sub>3</sub>, M<sub>4</sub>, M<sub>5</sub>, mACh,  $\alpha_1$ ,  $\alpha_2$ , H<sub>1</sub> or sigma receptors.

22. (new) The method of claim 21 in which A is the value for affinity at the 5-HT2A receptor.

23. (new) The method of claim 21 in which B is the value for affinity at the D2 receptor.

24. (new) The method of claim 20 in which the compound selected has  $Y \geq 2.00$ .

25. (new) A therapeutic product comprising a 5-HT2C receptor antagonist and a typical anti-psychotic, said product being a combined preparation for the treatment of schizophrenia, suicidality or mild cognitive impairment, wherein said antagonist and said anti-psychotic are administered simultaneously, separately or sequentially,

26. (new) A therapeutic product in which the 5-HT2C receptor antagonist is identifiable by the method of claim 20.

27. (new) A method for the treatment of a patient suffering from symptoms associated with a condition selected from the group consisting of negative symptoms of schizophrenia, cognitive dysfunction in schizophrenia, refractory schizophrenia, suicidality and mild cognitive impairment with a pharmaceutically effective amount of a

compound having a relative 5-HT<sub>2C</sub> affinity of  $\geq 1.80$ , wherein the relative 5HT<sub>2C</sub> affinity is determined according to the method of claim 20 with the proviso that:

(a) when the condition is selected from the group consisting of negative symptoms of schizophrenia, cognitive dysfunction in schizophrenia and refractory schizophrenia, the compound is other than ritanserin, clozapine, fluperlapine, loxapine, ORG-5222, pipamperone, sertindole, olanzapine, zotepine or ziprasidone;

(b) when the condition is selected from the group consisting of cognitive dysfunction in schizophrenia and mild cognitive impairment, the 5-HT<sub>2C</sub> receptor antagonist is other than (1R,2S,4R)-(-)-2-phenyl-2-(dimethylaminoethoxy)-1,7,7-trimethyl-bicyclo[2.2.1]heptane, (1R,2S,4R)-(-)-2-phenyl-2-(methylaminoethoxy)-1,7,7-trimethyl-bicyclo[2.2.1]heptane and pharmaceutically acceptable acid addition salts thereof; and

(c) when the condition is schizophrenic suicidality, the compound is other than clozapine.

28. (new) A method according to claim 27 wherein the condition is refractory schizophrenia, with the proviso that the compound is other than ritanserin, clozapine, fluperlapine, loxapine, ORG-5222, pipamperone, sertindole, olanzapine, zotepine or ziprasidone.

29. (new) A method according to claim 27 wherein the condition is suicidality, with the proviso that, when the suicidality is in a schizophrenic patient, the compound is other than clozapine.

30. (new) A method according to claim 29, wherein the suicidality is in a schizophrenic patient.

31. (new) A method according to claim 27 wherein the condition is mild cognitive impairment with the proviso that the compound is other than deramciclane or N-desmethylderamciclane.

32. (new) A method according to claim 27 wherein the compound is as described in a publication selected from the group consisting of WO 97/16429, WO 97/44334, US 05010078, EP 161,218, EP 401,707, EP 526,434, DE 02834114, EP 210,893, US 03580916, US 05043341, EP 620,222, EP 208,235, EP 437,790, DE 02614406, US 04338317, EP 271,013, EP 110,435, EP 398,326, WO 92/05170, WO 95/01976, WO 96/23783, WO 98/04289, WO 97/48700, WO 00/48602, WO 00/26186, WO 99/58490, WO 99/52517, WO 99/51237, WO 99/46245, WO 99/43319, WO 99/33841, WO 99/33840, WO 99/25356, WO 99/09017, WO 99/03833, WO 99/00119, WO 98/56367, WO 98/52943, WO 98/50358, WO 98/50346, WO 98/50343, WO 98/41527, WO 98/38165, WO 98/30561, WO 98/30546, WO 98/24785, WO 98/21958, WO 98/04261, WO 97/48699, WO 97/41858, WO 97/39001, WO 97/37989, WO

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EP 00375297, EP 00374042, EP 00373998, EP 00363963, EP 00354030, EP 00337136, EP 00332528, EP 00320983, EP 00218433 and EP 00145494.

33. (new) A method according to claim 27 in which the compound is selected from the group consisting of AHR-16303B (AH Robins Co. Inc), AP-792 and AT-1015 (Ajinomoto Co. Inc.), BMS-181102 (Bristol Myers Squibb), CV-5197 (Takeda Chemical Industries Ltd), dotarizine (Ferrer Internacional SA), E-2101 (Eisai Co Ltd), eltoprazine (Solvay SA), emopamil (Knoll AG), HT-90B (Chugai Pharmaceutical Co Ltd), ICI-169369 and ICI-170809 (Zeneca Group plc), LU-26042 and LU-29066 (H Lundbeck A/S), NPC-18166 (Scios Inc), Org-38457 (NV Organon), pelanserine (Cinvestav), perbufylline (Siegfried Group), SB-206553 and SB-242084 (SmithKline Beecham), SR-46615A (Sanofi Recherche SA), SUN-9221 (Suntory Ltd) tropoxin (Russian Academy Medical Science) and YM-992 (Yamanouchi Pharmaceutical Co Ltd).

34. (new) A method according to claim 27 in which the compound is selected from the group consisting of Ro-60-0759, RS-102221, SDZ-SER-082, ICI-169369, deramciclane, N-desmethyl-deramciclane, amesergide, sergolexole, CGS-18102A and LU-26042.

35. (new) A method according to claim 34 in which the compound is selected from the group consisting of deramciclane, N-desmethyl-deramciclane, amesergide, sergolexole, CGS-18102A and LU-26042.

36. (new) A method according to claim 27 wherein the condition is suicidality or mild cognitive impairment and wherein the compound is selected from the group consisting of ritanserin, clozapine, fluperlapine, loxapine, ORG-5222, pipamperone, sertindole, olanzapine, zotepine and ziprasidone, with the proviso that when the suicidality is in a schizophrenic patient, the compound is other than clozapine.

37. (new) A method for the treatment of a patient suffering from symptoms associated with a condition selected from the group consisting of refractory schizophrenia, suicidality and mild cognitive impairment with a pharmaceutically effective amount of a 5-HT<sub>2C</sub> receptor antagonist with the proviso that:

(a) when the condition is refractory schizophrenia, the 5-HT<sub>2C</sub> receptor antagonist is other than ritanserin, clozapine, fluperlapine, loxapine, ORG-5222, pipamperone, sertindole, olanzapine, zotepine or ziprasidone;

(b) when the condition is mild cognitive impairment, the 5-HT<sub>2C</sub> receptor antagonist is other than (1R,2S,4R)-(-)-2-phenyl-2-(dimethylaminoethoxy)-1,7,7-trimethyl-bicyclo[2.2.1]heptane, (1R,2S,4R)-(-)-2-phenyl-2-(methylaminoethoxy)-1,7,7-trimethyl-bicyclo[2.2.1]heptane and pharmaceutically acceptable acid addition salts thereof; and

(c) when the condition is schizophrenic suicidality, the 5-HT<sub>2C</sub> receptor antagonist is other than clozapine.



38. (new) A method according to claim 37 wherein the condition is refractory schizophrenia, with the proviso that the antagonist is other than ritanserin, clozapine, fluperlapine, loxapine, ORG-5222, pipamperone, sertindole, olanzapine, zotepine or ziprasidone.

39. (new) A method according to claim 37 wherein the condition is suicidality, with the proviso that, when the suicidality is in a schizophrenic patient, the 5-HT<sub>2C</sub> receptor antagonist is other than clozapine.

40. (new) A method according to claim 39, wherein the suicidality is in a schizophrenic patient.

41. (new) A method according to claim 37 wherein the condition is mild cognitive impairment with the proviso that the antagonist is other than deramciclane or N-desmethylderamciclane.

42. (new) A method according to claim 37 wherein the 5-HT<sub>2C</sub> receptor antagonist is as described in a publication selected from the group consisting of WO 97/16429, WO 97/44334, US 05010078, EP 161,218, EP 401,707, EP 526,434, DE 02834114, EP 210,893, US 03580916, US 05043341, EP 620,222, EP 208,235, EP 437,790, DE 02614406, US 04338317, EP 271,013, EP 110,435, EP 398,326, WO 92/05170, WO 95/01976, WO 96/23783, WO 98/04289, WO 97/48700, WO 00/48602,

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43. (new) A method according to claim 37 in which the 5-HT<sub>2C</sub> receptor antagonist is selected from the group consisting of AHR-16303B (AH Robins Co. Inc), AP-792 and AT-1015 (Ajinomoto Co. Inc.), BMS-181102 (Bristol Myers Squibb), CV-5197 (Takeda Chemical Industries Ltd), dotarizine (Ferrer Internacional SA), E-2101 (Eisai Co Ltd), eltoprazine (Solvay SA), emopamil (Knoll AG), HT-90B (Chugai Pharmaceutical Co Ltd), ICI-169369 and ICI-170809 (Zeneca Group plc), LU-26042 and LU-29066 (H Lundbeck A/S), NPC-18166 (Scios Inc), Org-38457 (NV Organon), pelanserin (Cinvestav), perbufylline (Siegfried Group), SB-206553 and SB-242084 (SmithKline Beecham), SR-46615A (Sanofi Recherche SA), SUN-9221 (Suntory Ltd) tropoxin (Russian Academy Medical Science) and YM-992 (Yamanouchi Pharmaceutical Co Ltd).

44. (new) A method according to claim 37 in which the 5-HT<sub>2C</sub> receptor antagonist is selected from the group consisting of Ro-60-0759, RS-102221, SDZ-SER-

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082, ICI-169369, deramciclane, N-desmethyl-deramciclane, amesergide, sergolexole, CGS-18102A and LU-26042.

45. (new) A method according to claim 44 in which the 5-HT<sub>2C</sub> receptor antagonist is selected from the group consisting of deramciclane, N-desmethyl-deramciclane, amesergide, sergolexole, CGS-18102A and LU-26042.

46. (new) A method according to claim 37 wherein the condition is suicidality or mild cognitive impairment and wherein the 5-HT<sub>2C</sub> receptor antagonist is selected from the group consisting of ritanserin, clozapine, fluperlapine, loxapine, ORG-5222, pipamperone, sertindole, olanzapine, zotepine and ziprasidone, with the proviso that when the suicidality is in a schizophrenic patient, the 5-HT<sub>2C</sub> receptor antagonist is other than clozapine.

47. (new) A product according to claim 25 in which the 5-HT<sub>2C</sub> receptor antagonist is as described in a publication selected from the group consisting of WO 97/16429, WO 97/44334, US 05010078, EP 161,218, EP 401,707, EP 526,434, DE 02834114, EP 210,893, US 03580916, US 05043341, EP 620,222, EP 208,235, EP 437,790, DE 02614406, US 04338317, EP 271,013, EP 110,435, EP 398,326, WO 92/05170, WO 95/01976, WO 96/23783, WO 98/04289, WO 97/48700, WO 00/48602, WO 00/26186, WO 99/58490, WO 99/52517, WO 99/51237, WO 99/46245, WO 99/43319, WO 99/33841, WO 99/33840, WO 99/25356, WO 99/09017, WO 99/03833,

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48. (new) A product according to claim 25 in which the 5-HT<sub>2C</sub> receptor antagonist is selected from the group consisting of AHR-16303B (AH Robins Co. Inc), AP-792 and AT-1015 (Ajinomoto Co. Inc.), BMS-181102 (Bristol Myers Squibb), CV-5197 (Takeda Chemical Industries Ltd), dotarizine (Ferrer Internacional SA), E-2101 (Eisai Co Ltd), eltoprazine (Solvay SA), emopamil (Knoll AG), HT-90B (Chugai Pharmaceutical Co Ltd), ICI-169369 and ICI-170809 (Zeneca Group plc), LU-26042 and LU-29066 (H Lundbeck A/S), NPC-18166 (Scios Inc), Org-38457 (NV Organon), pelanserine (Cinvestav), perbufylline (Siegfried Group), SB-206553 and SB-242084 (SmithKline Beecham), SR-46615A (Sanofi Recherche SA), SUN-9221 (Suntory Ltd) tropoxin (Russian Academy Medical Science) and YM-992 (Yamanouchi Pharmaceutical Co Ltd).

49. (new) A product according to claim 25 in which the 5-HT<sub>2C</sub> receptor antagonist is selected from the group consisting of Ro-60-0759, RS-102221, SDZ-SER-082, ICI-169369, deramciclane, N-desmethyl-deramciclane, amesergide, sergolexole, CGS-18102A and LU-26042.

50. (new) A product according to claim 25 in which the 5-HT<sub>2C</sub> receptor antagonist is selected from the group consisting of deramciclane, N-desmethyl-deramciclane, amesergide, sergolexole, CGS-18102A and LU-26042.

51. (new) A product according to claim 25 in which the 5-HT<sub>2C</sub> receptor antagonist is selected from the group consisting of ritanserin, clozapine, fluperlapine, loxapine, ORG-5222, pipamperone, sertindole, olanzapine, zotepine and ziprasidone, with the proviso that when the suicidality is in a schizophrenic patient, the 5-HT<sub>2C</sub> receptor antagonist is other than clozapine.